Message

From: Lin, Yu-Sheng [Lin.Yu-Sheng@epa.gov]
Sent: 11/20/2018 6:07:54 PM
To: Bahadori, Tina [Bahadori.Tina@epa.gov]; Bussard, David [Bussard.David@epa.gov]; Thayer, Kris [thayer.kris@epa.gov]; Schlosser, Paul [Schlosser.Paul@epa.gov]; White, Paul [White.Paul@epa.gov]; Wright, Michael [Wright.Michael@epa.gov]; Bateson, Thomas [Bateson.Thomas@epa.gov]; Vandenberg, John [Vandenberg.John@epa.gov]; Ramasamy, Santhini [Ramasamy.Santhini@epa.gov]; Morozov, Viktor [Morozov.Viktor@epa.gov]; Brown, James [Brown.James@epa.gov]
CC: Garcia, Kelly [garcia.kelly@epa.gov]
Subject: RE: PBPK models for Manganese discussion (Updated with materials)

Hi Tina and All

This is the response to your earlier question and David's question, not for the summary of meeting notes. I did not have additional comments about the notes.

Ex. 5 Deliberative Process (DP)

Happy Thanksgiving.

Regards

Yu-Sheng

From: Bahadori, Tina
Sent: Tuesday, November 20, 2018 12:25 PM
To: Lin, Yu-Sheng <Lin.Yu-Sheng@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; White, Paul <White.Paul@epa.gov>; Wright, Michael <Wright.Michael@epa.gov>; Bateson, Thomas <Bateson.Thomas@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Brown, James <Brown.James@epa.gov>
Cc: Garcia, Kelly <garcia.kelly@epa.gov>
Subject: RE: PBPK models for Manganese discussion (Updated with materials)

Hi Yu-Sheng,

Ex. 5 Deliberative Process (DP)

Tina

From: Lin, Yu-Sheng
Sent: Tuesday, November 20, 2018 12:13 PM
To: Bussard, David <Bussard.David@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; White, Paul <White.Paul@epa.gov>; Wright, Michael <Wright.Michael@epa.gov>; Bateson, Thomas <Bateson.Thomas@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Brown, James <Brown.James@epa.gov>
Cc: Garcia, Kelly <garcia.kelly@epa.gov>
Subject: RE: PBPK models for Manganese discussion (Updated with materials)

Ex. 5 Deliberative Process (DP)

Regards,

Yu-Sheng

TABLE 3

Mean (± SEM) Tissue Manganese Concentrations (μg Mn/g Tissue Wet Weight) in Young Monkeys following Subchronic Exposure to Either Air or $MnSO_4$

	Nominal $MnSO_4$ concentration (mg Mn/m^3)			
	Air	0.06	0.3	1.5
Olfactory tissues				
Olfactory epithelium[a]	0.42 ± 0.01	1.22 ± 0.15*	2.96 ± 0.46*	7.10 ± 2.01*
Olfactory bulb	0.31 ± 0.01	0.77 ± 0.04*	1.36 ± 0.15*	2.40 ± 0.18*
Olfactory tract	0.30 ± 0.06	0.43 ± 0.02	0.61 ± 0.05*	1.12 ± 0.08*
Olfactory cortex	0.19 ± 0.004	0.27 ± 0.02*	0.31 ± 0.01*	0.42 ± 0.01*
Brain				
Globus pallidus[a]	0.48 ± 0.04	0.80 ± 0.04*	1.28 ± 0.15*	2.94 ± 0.23*
Putamen	0.36 ± 0.01	0.58 ± 0.04*	0.75 ± 0.05*	1.81 ± 0.14*
Caudate	0.34 ± 0.02	0.47 ± 0.04	0.69 ± 0.03*	1.72 ± 0.10*
White matter	0.17 ± 0.01	0.25 ± 0.01*	0.39 ± 0.04*	0.87 ± 0.08*
Frontal cortex	0.25 ± 0.03	0.29 ± 0.02	0.29 ± 0.01	0.47 ± 0.02*
Cerebellum[a]	0.44 ± 0.01	0.62 ± 0.02*	0.70 ± 0.04*	1.10 ± 0.11*
Pituitary	0.84 ± 0.12	1.53 ± 0.25	2.43 ± 0.13*	6.19 ± 0.61*
Trigeminal nerve	0.17 ± 0.05	0.17 ± 0.01	0.21 ± 0.01	0.42 ± 0.08*
Organs				
Femur	0.13 ± 0.02	0.11 ± 0.01	0.13 ± 0.03	0.20 ± 0.03
Heart	0.16 ± 0.03	0.33 ± 0.03*	0.49 ± 0.03*	0.62 ± 0.05*
Kidney	1.14 ± 0.12	1.43 ± 0.05	1.86 ± 0.14*	2.61 ± 0.30*
Liver	2.49 ± 0.09	2.91 ± 0.18	3.17 ± 0.20	3.52 ± 0.45*
Lung	0.15 ± 0.03	0.18 ± 0.01	0.25 ± 0.02*	0.33 ± 0.04*
Pancreas	1.59 ± 0.11	1.72 ± 0.09	2.34 ± 0.11*	2.95 ± 0.24*
Skeletal muscle[a]	0.15 ± 0.03	0.12 ± 0.03	0.18 ± 0.02	0.58 ± 0.19*
Parietal bone[a]	0.08 ± 0.04	0.05 ± 0.02	0.13 ± 0.06	0.25 ± 0.04*
Testis	0.26 ± 0.03	0.35 ± 0.03	0.40 ± 0.05	0.39 ± 0.07
Fluids				
Bile[a]	0.89 ± 0.22	1.65 ± 0.31	3.78 ± 0.34*	7.60 ± 1.68*
Blood	0.010 ± 0.001	0.015 ± 0.002	0.022 ± 0.003*	0.026 ± 0.003*
Urine[a]	0.000 ± 0.000	0.001 ± 0.000	0.005 ± 0.003*	0.005 ± 0.001*
Group size (n)	6	6	4	4

------- Estimation of minimum airborne Mn to cause significant increase in brain Mn (Dorman 2006 Monkey data) --------

The goal: To estimate airborne Mn at or above which the corresponding brain Mn will arise significantly higher than background Mn (e.g., due to dietary Mn) using backward calculation. This method doesn't use any PK model.

Methods:

The following are the logic/steps:

(1) Assume the relationship of airborne Mn with Mn in Globus Pallidus is linear between lowest two airborne levels (Air where Mn=0 and 0.06 mg/m3) (see circled graph from our Appendix B, Table 3 is from Dorman 2006, monkey data).

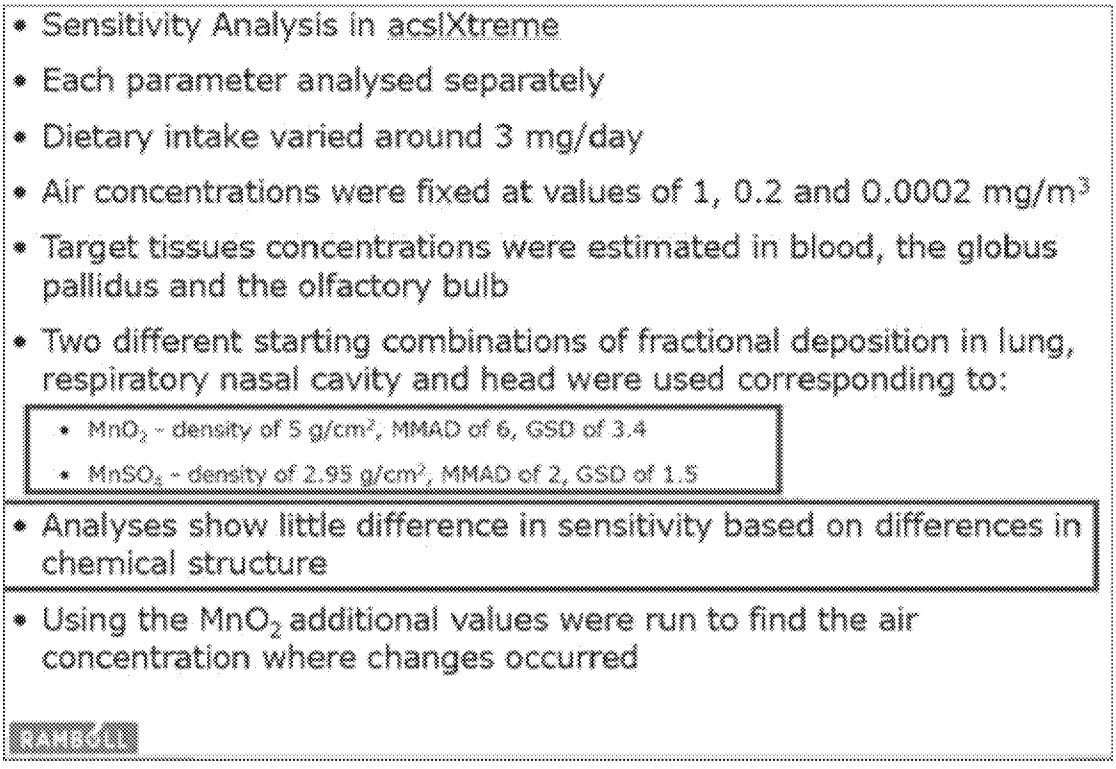
(2) Then I estimated the minimum levels of Mn Globus Pallidus (0.606 mg Mn/g), which is statistically different from background Mn in Globus Pallidus (0.48 mg Mn/g). The sample size is 6 for each group and standard error of mean is the same (0.04) for both as you can see in Dorman 2006. Thus, I also assume it is 0.04 mg/g for estimated 0.606 mg/g. I used GraphPad (GraphPad QuickCalcs: t test calculator)

(3) Then I used Excel and the data from lowest two airborne levels (airborne Mn = 0 and 0.06 mg/m3) and corresponding Globus Pallidus (0.48 and 0.8 mg Mn/g), respectively to do backward calculation and estimate what airborne Mn level can cause 0.606 mg Mn/g). The answer would be about 0.0236 mg/m3.

With the adjustment of uncertainty factor of 100 (10 for population variability and 10 for data limitation/uncertainty), it will bring down to 0.000236 mg/m3 (that is in the range of our RfD estimate)

The value (0.000236 mg/m3) could become even smaller if the sample size is bigger (> 6 monkeys per group).

Of note, they also mention that there is no significant difference in sensitivity analysis between MnO2 and MnSO4



From: Bussard, David
Sent: Tuesday, November 20, 2018 10:07 AM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; White, Paul <White.Paul@epa.gov>; Lin, Yu-Sheng <Lin.Yu-Sheng@epa.gov>; Wright, Michael <Wright.Michael@epa.gov>; Bateson, Thomas <Bateson.Thomas@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Morozov, Viktor

<Morozov.Viktor@epa.gov>; Brown, James <Brown.James@epa.gov>
Cc: Garcia, Kelly <garcia.kelly@epa.gov>
Subject: RE: PBPK models for Manganese discussion (Updated with materials)

Ex. 5 Deliberative Process (DP)

David

From: Bahadori, Tina
Sent: Tuesday, November 20, 2018 6:42 AM
To: Thayer, Kris <thayer.kris@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; White, Paul <White.Paul@epa.gov>; Lin, Yu-Sheng <Lin.Yu-Sheng@epa.gov>; Wright, Michael <Wright.Michael@epa.gov>; Bateson, Thomas <Bateson.Thomas@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Brown, James <Brown.James@epa.gov>
Cc: Garcia, Kelly <garcia.kelly@epa.gov>
Subject: RE: PBPK models for Manganese discussion (Updated with materials)

Thanks Kris. I added some comments to your notes. Mainly I suggested:

Ex. 5 Deliberative Process (DP)

T.

From: Thayer, Kris
Sent: Tuesday, November 20, 2018 1:31 AM
To: Garcia, Kelly <garcia.kelly@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>; White, Paul <White.Paul@epa.gov>; Lin, Yu-Sheng <Lin.Yu-Sheng@epa.gov>; Wright, Michael <Wright.Michael@epa.gov>; Bateson, Thomas <Bateson.Thomas@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Bussard, David <Bussard.David@epa.gov>; Ramasamy, Santhini <Ramasamy.Santhini@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Lavoie, Emma <Lavoie.Emma@epa.gov>
Subject: RE: PBPK models for Manganese discussion (Updated with materials)

I wanted to get some feedback on this meeting summary that would be posted on the IRIS site before posting…and I guess we should share for quick review as a courtesy with other EPA attendees who aren't part of the core team. Apologies if I missed anyone – this list was culled from recipients of the meeting invite.

Summary of Meeting Action Items

Event Title: Manganese (Mn) Physiologically based pharmacokinetic (PBPK) Modeling Updates
Date: November 20, 2018
Time: 9:00 PM – 12:00 PM
Keywords: IRIS, Manganese

Attendees:
THIS IS STOLEN FOR CHLOROPRENE and is only a partial, Kris has Kelly to update
Harvey Clewell - Ramboll
Tina Bahadori – US, EPA, NCEA
Tom Bateson – US, EPA, NCEA
David Bussard – US, EPA, NCEA
Yu-Sheng Lin– US, EPA, NCEA
Viktor Morozov– US, EPA, NCEA
Paul Schlosser – US, EPA, NCEA
Santhini Ramasamy– US, EPA, NCEA
Kris Thayer – US, EPA, NCEA
John Vandenberg – US, EPA, NCEA
Mike Wright– US, EPA, NCEA

Summary of meeting activities and next steps:

Ex. 5 Deliberative Process (DP)

-----Original Appointment-----
From: Garcia, Kelly
Sent: Tuesday, October 30, 2018 10:47 AM
To: Garcia, Kelly; Schlosser, Paul; Thayer, Kris; Brown, James; Boyes, William; Jarabek, Annie; White, Paul; Hoyer,

Marion; Lin, Yu-Sheng; Wright, Michael; Bateson, Thomas; Vandenberg, John; Ex. 6 Personal Privacy (PP) Ramasamy, Santhini
Cc: Morozov, Viktor; Bussard, David; rgentry@ramboll.com; cvanlandingham@ramboll.com; Kenyon, Elaina; Cook, Rich; Sopata, Joe; Smith, Darcie
Subject: PBPK models for Manganese discussion (Updated with materials)
When: Friday, November 16, 2018 9:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: DCRoomRRB51109-1

Good morning,

Paul Schlosser has requested that I hold this time for a meeting between EPA and the team developing PBPK models for Manganese. Please find the agenda and logistics below.

Agenda

1. Welcome from Kris Thayer, U.S. EPA
2. EPA Quality Assurance Project Plan (QAPP) for PBPK Models, Paul Schlosser, U.S. EPA
3. Background on Mn PBPK models, Mel Andersen, private consultant
4. New work on Mn PBPK models, Mel Andersen and colleagues
    a. Adding drinking water as a route of entry
    b. Developing a model with rapid tissue binding/dissociation rate constants
    c. Sensitivity analysis for PBPK models

Meeting logistics

Rooms: DC 51109-1 (5th floor fishbowl); RTP B-249
Call in number: Ex. 6 Personal Privacy (PP)
Pi Ex. 6 Personal Privacy (PP)
Adobe Connect webinar: Ex. 6 Personal Privacy (PP)